<u>Comments of Dr. Woodhall Stopford of Duke University Medical Center.</u>

You have asked for comments concerning your above summary. You based your Inhalation Reference Exposure Level (iREL) for respirable crystalline silica on the study of Hnizdo & Sluis-Cremer (1993), corrected for the average crystalline silica content they reported for South African gold mines. This study was supported by dose-response relationships between crystalline silica and silicosis noted by several studies, the availability of several long-term worker exposure studies at various concentration ranges and the observation of no adverse effect levels for respirable crystalline silica reported in some studies. I am concerned that you corrected the Hnizdo & Sluis-Cremer study without comment concerning the relationship between the dust exposures they measured in their study (combusted, acid-washed respirable dust) and your correction for silica in respirable dust; your choice of setting an iREL against dust that falls within a range that can deposit anywhere in the thoracic region as apposed to respirable dust; and the lack of discussion, or correction in your iREL assessment, for bias created by choosing a mass median aerodynamic diameter (MMAD) that is appreciably larger than used in the epidemiological studies you used for the development if the iREL such that excessively large crystalline silica content of samples representing the MMAD would be expected..

<u>Comment 1</u>. <u>Correction of iREL for quartz content of respirable dust.</u> Hnizdo & Sluis-Cremer (1993) base their risk assessment on exposure to acid washed and combusted respirable dust. They comment that this treatment results in respirable dust that is mainly made up of crystalline silica and silicates. They comment that respirable dust in South African gold mines contains an average of 30% quartz. This dust, however, likely represents untreated dust. Your correction, therefore, is likely to make your iREL unduly conservative. Without the correction, the iREL would be closer to that expected if you used the Hughes, et al. (1998) analysis. With the correction your iREL is closer to that you would expect if you use the Steenland & Brown (1995) analysis. You may want to either take USEPA's approach and base your iREL on a number of studies or comment on whether or not the likely error introduced by correcting for respirable quartz content of mine dusts is acceptable.

<u>Response</u>. *In regard to the commentator's second concern, exposure estimates, OEHHA staff has reviewed the paper by Gibbs and Du Toit (2002) for possible application to the cREL derivation. Acceptance of the Gibbs and Du Toit analysis would change the percent quartz in the South African gold mine dust from 30% to 54%. However, Gibbs and Du Toit (2002) also cite the work of Kielblock and coworkers (1997) indicating that recent measurements of mine dust indicate 15% respirable quartz content. (Kielblock AJ, Franz RM, Unsted AD, van der Linde A, Ashworth SGE. 1997. Quantification of occupational health risks in the South African mining industry and assessment of sources of uncertainty in the estimates. Final project report. Project no. SIMRISK 401. Safety in Mines Research Advisory Committee. Johannesburg: CSIR Division of Mining Technology).*

Kielblock et al. (1997) studied an unspecified number of South African gold mines with a total employment of approximately 300,000 underground and surface workers.

For 223,104 mineworkers sampled during 1996, the average respirable dust exposure was 412 µg/m^3 (Table 4.3.1a). Among 137,439 mineworkers sampled for alpha-quartz, the average alpha-quartz exposure was 62.5 µg/m^3 (Table 4.3.1b). The average percent alpha-quartz in the respirable dust was therefore 15.08%. The percent alpha quartz concentration in the dust ranged from 0-5% for approximately 10% of the miners to >40% for approximately only 1% of the miners (Figure 4.3.3j). The data of Kielblock et al. (1997) indicate that few miners have recently been exposed to 54% quartz.

In a personal communication, Dr. Eva Hnizdo, now with the U.S. National Institute of Occupational Safety and Health (NIOSH), provided a summary of various other estimates that have been made. "Past surveys indicate that the amount of airborne respirable dust in SA gold mines in 1980's and in 1970's was on average around 0.4 mg/m^3 with average quartz concentration of 0.08 mg/m^3 (about 20%)." She also mentions a Ph.D. thesis (unpublished) by R.E.G. Rendall, in which the silica percentage averaged 22% during the period from 1956 to 1972, which overlaps the period of the 1960s studied by Beadle (1971). Thus OEHHA staff is reluctant to accept only the highest value available (54%) for % quartz in the mine dust. We have used the value provided in the original paper by Hnizdo and Sluis-Cremer which falls about mid-range of available estimates.

Gibbs and Du Toit (2003) state that the percent quartz in the South African gold mine dust in the Hnizdo and Sluis-Cremer (1993) study should be increased by a factor of 1.8 (54% rather than 30%). ("In the absence of systematic side-by-side thermal precipitator and modern respirable mass measurements in the South African gold mines, the true relationship between the respirable mass concentrations and the theoretically derived concentrations cannot be known. However, with many uncertainties, we estimate that the quartz exposures of South African miners derived from past theoretically based conversions from particle number to respirable mass underestimate the actual quartz exposures by a factor of about 2." Two was rounded up from 1.8 in the text.) Mine dust samples are heat treated (pyrolysed) to remove organics and treated with hydrochloric acid to remove acid-soluble materials before the heat resistant, acid insoluble silica particles are quantified. According to Hnizdo (personal communication, 2004), "the issue Gibbs pointed out is that the respirable dust concentration was measured after acid treatment by hydrochloric acid. Hydrochloric acid may dissolve some components of the respirable dust and increases the concentration of silica. The uncertainty is how much did the hydrochloric acid dissolve. I was told that the acid was used to allow them to measure the surface area and count the particles under the microscope." OEHHA staff does not know how much material the hydrochloric acid dissolved and Gibbs and Du Toit admit there is much uncertainty in their estimate. Given the uncertainty in their estimate and the variability in percent quartz given by various samplings of the dust, OEHHA staff does not believe that there is a compelling case to take the highest estimate available.

Comment 2. Use of inhalable vs respirable dust for your iREL**.** ACGIH (1998) defines thoracic particulate mass as that dust with MMAD of 10 µm. They note that it is an appropriate descriptor for exposure to dusts from those materials that are hazardous when deposited anywhere within the airways and the gas-exchange region of the lungs. Materials that cause both airway irritation and lung effects, such as sulfur dioxide, would be appropriate to monitor using this parameter. On the other hand, they define respirable particle mass (respirable dust) as that dust with a MMAD of 4.0 μm. They note that this measurement should be used for those materials that are hazardous when deposited in the gas-exchange region. This latter definition is in accord with the International Organization/European Standardization Committee protocol for measurement of respirable dust. You have chosen to use an iREL based upon measurements of thoracic particle mass, instead of respirable dust. An iREL based upon the latter may be more appropriate. Hearl (1997) notes that measurements of respirable dust, as defined by ACGIH and ISO, are intended to apply to health-related sampling both in the workplace and general environment.

Raabe (1982) notes that "particle size-related standards are necessary to provide more meaningful measurements for both source emission control and environmental monitoring where the lung is the principal organ of concern…'[I]nhalable' particle sampling would tend to obscure the contribution to environmental aerosols of smaller, more respirable and stable particles that are of primary importance in potential risks to pulmonary and small bronchial airways." Respirable crystalline silica certainly falls in this paradigm: quartz particles that will produce silicosis are those that deposit in the smallest airways (bronchioles) and alveoli.

Your iREL is not only more appropriately represented by measures of respirable crystalline silica but will be strengthened by such a change. I have reviewed the industrial hygiene measures used as a basis for risk assessment for the relationship between exposure to crystalline silica and silicosis in the studies outlined in the table below and reviewed in your Chronic Toxicity Summary. In each instance measurements either were of respirable dust or silica or converted to respirable dust or silica. In most instances the norm was either the ACGIH or ISO standard where respirable dust collectors collected particles with a MMAD of 4.0 μm. In two studies respirable particle counts where the particle diameters were 5 μm or less were converted to respirable dust mass exposure without comparison to a cyclone which collected particles with a MMAD of 4.0 μm. In these instances the MMAD of the particles might be expected to be <6 μm, the MMAD of respirable particle counts above a geometric mean of 3 μm (Rando et al, 2001). An iREL based on a MMAD of 4.0 would be supported by studies upon which you based your iREL determination and would make your iREL a true health effects-based iREL.

Table: Respirable dust measurement methods in epidemiological studies relating exposure to risk of silicosis

Study	**Quartz measurement**	**Median respirable mass fraction**	**Reference**
Ontario hard rock miners	Cyclone and conversion of konimeter counts to respirable mass by comparison	4 µm	Muir et al ’89, Verma et al ‘89
Gray iron foundry workers	Conversion of respirable dust counts to respirable mass and multiplication by bulk silica %	<6 µm	Rosenman et al ‘96
Diatomaceous earth workers	Cyclone, total dust and respirable dust counts with conversion of latter to respirable mass by comparison	4 µm	Hughes et al ’98, Seixas et al ‘97
South African gold miners	Integrated respirable dust counts and surface area to get respirable mass	<6 µm	Hnizdo & Sluis-Cremer ‘93
Scotish coal workers	Integrated measurements of respirable dust and settled dust silica levels	4 µm	Miller et al ‘98
South Dakota gold miners	Respirable dust mass and conversion of respirable dust counts to respirable mass by comparison	4 µm	Steenland & Brown ‘95
Leadville miners	Assignment of representative respirable silica levels to respirable dust exposure measurements	4 µm	Kreiss & Zhen ‘96
Chinese tin miners	Cyclone and conversion of total dust mass to respirable mass by comparison	4 µm	Chen et al ‘01
Industrial sand workers	Cyclone and conversion of respirable dust counts to respirable mass by comparison	4 µm	Rando et al ‘01

Response. *OEHHA staff is proposing a chronic inhalation REL for respirable, crystalline silica. The Table provided by the commentator shows that respirable, as used in many epidemiological studies of silica, means a 50% cut point at 4 µm. Hnizdo and Sluis-Cremer (1993) based their study on similar silica particle measurements (< 6 µm).. The implication for the cREL is that using the silica content of PM_{10} as the measurement of near-source ambient concentration resulting from Hot Spot facility emissions includes many larger silica particles that probably do not get into the deep lung and thus purportedly do not contribute to silicosis, but they inflate the Hazard Index.*

*OEHHA staff agrees that the silica particles should be 'respirable'. California EPA defines 'respirable' as particles 10 µm or less in MMAD. The selection of the 10 µm or less MMAD criterion is consistent with this intention, and also reflects the fact that this type of sampler (for "PM_{10}") is the one used for ambient air sampling in the general environment. Colleagues in the California Air Resources Board advise us that the NIOSH-specified personal samplers used in many occupational studies have not been validated for the combination of sensitivity, sampling duration, and operating conditions required for environmental measurements. We agree that there are differences in the size range distribution between a typical PM_{10} measuring device and that used by the investigators in the epidemiological studies. Clearly the level of confidence in the derived health protective level is greatest for materials where the particle size (and reactivity) are similar to those seen in the occupational studies. The NIOSH samplers used in the epidemiological studies captured particles in a size range where the median of the distribution was 4 µm; thus half the particles were larger than that. These samplers are meant to mimic the size range of particles that reach into the bronchiolar and alveolar spaces (what the occupational community calls respirable). PM_{10} samplers are meant to capture particles that deposit along the entire respiratory tree including those that deposit in the tracheo-bronchial, and alveolar regions. Deposition by particle size is complex, and is dependent on the aerodynamic diameter, hygroscopicity, and electrostatic charge of the particles, and on a number of host factors including airway structure and geometry, as well as depth, rate, and mode of breathing (nasal vs. oronasal). The fractional deposition in the various regions of the respiratory tract is not linear with respect to size. Generally, though, larger particles impact higher in the respiratory tree (the extrathoracic and tracheobronchial regions), while smaller particles show greater deposition in the lower tracheo-bronchial and alveolar regions. There are a number of models of regional deposition in the respiratory tract as well as some measurements. Chan and Lippman (*Am Ind Hyg Assoc J. 41:399-409, *1980) showed peak alveolar deposition for particles about 3 µm MMAD with deposition dropping above and below that. Their data and model indicate tracheobronchial deposition rises rapidly above about 3 µm MMAD. Data also indicate significant interindividual variability in fractional deposition. The ICRP (1994) model used in evaluating risk from radioactive particles indicates that total deposition in the respiratory tract for particles 3 µm in activity median thermodynamic diameter (AMTD) is about 0.78 with a regional deposition fraction of 0.077 for the alveolar region for a reference male worker during nasal breathing. The same model predicts a total deposition in the respiratory tract of 0.77 for 10 µm AMTD particles and a deposition fraction of 0.024 in the alveolar region. Clearly 10 µm particles get into the alveolar space. A smaller difference in regional deposition is predicted for mouth breathers. Thus, only considering the size range measured by the samplers used in the studies actually underestimates the amount of silica that can get deposited in the gas exchange regions of the lung. Although it is frequently assumed that the silicosis is induced by that fraction of the silica that reaches the alveolus, we don't have data that clearly indicates no concern for the coarser fraction of particles captured by PM_{10} measurements.*

Another complication in determining the particle size range to which the REL should apply is the fact that we do not have data on the particle size distribution from all the *epidemiological studies or from sources of crystalline silica in the ambient air from facilities in the Hot Spots program. It is unfortunate that we do not have better data on the particle size distribution of various sources of crystalline silica particles. That would allow a more certain comparison between typical ambient source exposures that the Hot Spots program would evaluate (e.g., diatomaceous earth processing plants, quarries, mines) with occupational sources such as the mines evaluated in the studies. It seems likely that the industrial sources of concern produce smaller crystalline silica particles than blowing crustal material.*

All things considered, although the fractional deposition of coarser particles is less in the lower airway, such particles clearly can enter the bronchioles and alveoli. We do not believe that applying the chronic REL to silica captured in a PM_{10} sampler will result in a gross overestimation of the hazard index from industrial sources of silica.

Comment 3. Relationship of crystalline silica content to MMAD of dusts**.** Quartz content of soil-related dusts (the major source of crystalline silica in rural and agricultural regions, USEPA 1996) increases as particle size increases. We (Stopford & Stopford, 1995) found that the quartz content of clay-containing soils that passed through a 45 mesh sieve (MMAD ranging from 7.7 to 58.9 μm) ranged from 17.5 to 52.0% while the quartz content of 4 μm fraction of these same soils ranged 1.3 to 3.4%, values averaging 14 fold less than for the course soil. Similarly, Davis et al (1984) when comparing the course (*sic*) (>2.5 μm cut) and fine (<2.5 μm cut) fractions of PM10 samples found that the quartz content of the course fractions averaged 4.9% while those of the fine fractions averaged 0.4%, 12 fold less than the average quartz content of the course fraction. USEPA (1996) re-analyzed this data and found that the quartz content of the fine fraction had a geometric mean concentration of 0.1% and that of the course fraction a geometric mean concentration of 7.2%. For the California cities in the Davis et al (1984) study, the respirable quartz content of the course fraction ranged from 1.9 to 6.0% and for the fine fraction from non-detectable to 1.0%. Chow et al (1993) found a similar relationship in analyzing the PM10 and PM2.5 silicon values in samples collected in cities in the San Joaquin Valley. The PM10 silicon values averaged from 5.2 to 8.7 $\mu g/m^3$ while PM2.5 silicon values averaged from 0.33 to 0.82 $\mu g/m^3$. PM10 samples have a MMAD of about 8 μm (McClellan & Miller, 1997). Using a MMAD of 10 μm would further exaggerate the crystalline silica content of environmental samples, unduly weighing the quartz content of the non-respirable fraction of samples collected to represent the 10 μm MMAD distribution. Basing your iREL for respirable quartz on a particle distribution with a MMAD of 4 μm would avoid this bias.

Response. *The chronic REL for crystalline silica will be applied to modeled or measured crystalline silica in the PM10 size range emitted from Hot Spots facilities, not to a measure of PM10. Thus the varying silica content of PM10 either urban, rural, or from a specific source is not relevant to the development or application of the chronic REL.*

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